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Frontal Cortex TMS for Tinnitus

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ABSTRACT

Both invasive and non-invasive neuromodulation of the dorsolateral prefrontal cortex (DLPFC) are capable of suppressing tinnitus loudness. Repetitive transcranial magnetic stimulation (rTMS) of the DLPFC has an add-on effect for auditory cortex (AC) rTMS in improving tinnitus-related distress. We aimed to investigate whether TMS and rTMS of the DLPFC is capable of reducing tinnitus loudness and what mechanism might be involved. Two TMS studies targeting the right DLPFC were performed. Study 1 investigated 44 tinnitus patients who underwent either 1 or 10 Hz real or sham TMS (200 pulses at 80% motor threshold). In Study 2 we performed rTMS (10 sessions of 600 pulses) in responders of study 1. Changes on the visual analog scale (VAS) loudness were evaluated. All patients underwent a pre-TMS electroencephalography: differences in functional connectivity between responders and non-responders were evaluated using sLORETA. Only 1 Hz TMS was capable of significantly reducing tinnitus loudness for 11 patients with a mean suppression of 39.23%. RTMS for these 11 patients yielded a 21% improvement in VAS loudness, and in 7 of 11 rTMS was successful, with, a mean suppression of 27.13%. The responders were characterized by a difference in lagged linear connectivity in the theta band among the DLPFC, anterior cingulate cortex (ACC), parahippocampus and AC. In summary, 1 H, TMS and rTMS of the right DLPFC can transiently reduce the perceived tinnitus loudness mediated via functional connections between the DLPFC and a network consisting of the ACC, parahippocampus and AC.

Introduction

Tinnitus is the perception of a sound in the absence of any external physical sound source [27]. In western societies about 5–15% of the population has chronic tinnitus [3,25], and in 2.4% of the population tinnitus is severely debilitating [3], leading to distress [2], depression [42], cognitive dysfunctioning [23] and insomnia [10].

Based on functional imaging studies, it is generally accepted that tinnitus is related to maladaptive plasticity of the auditory system, involving functional reorganization and hyperactivity in the auditory central nervous system [18,29,55,69] with co-activation of non-auditory brain structures such as the insula [74,81], anterior cingulate cortex [53,67,81], and dorsolateral prefrontal cortex (DLPFC) [53,81].

It has recently been proposed that the unified tinnitus percept actually involves multiple parallel dynamically adaptive networks [11], with each network reflecting a specific aspect of tinnitus, for example distress [13,81]. These subnetworks can be non-specific as demonstrated by the fact that the distress network in tinnitus is similar to the distress network observed in pain [51], asthmatic dyspnea [90], social rejection [45] and somatoform disorder [39].

The DLPFC has been proposed as an integrator of emotion and cognition [22]. The DLPFC seems to play a significant role in auditory processing as well. It has direct connections to the auditory cortex as well as indirect via the posterior orbitofrontal cortex (OFC) and is implicated in selecting salient auditory signals and suppressing distractors via its projections to the reticular nucleus of the thalamus [4]. This selection mechanism involves the right DLPFC, the dorsal anterior cingulate and posterior parietal area [68]. Thus when salient auditory stimuli are presented the DLPFC activates the pathway of the relevant sensory modality, i.e. the auditory system, and inhibits the non-relevant sensory modality pathway, e.g. the visual system [7]. However, via the same mechanism, the DLPFC can also exert an inhibitory modulation of input to primary auditory cortex [35]. This selection mechanism explains the DLPFC's

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involvement in auditory attention [1,43,88] via a top-down modulation of auditory processing [49]. In addition to selecting salient sensory processing, the DLPFC also has a facilitatory effect on auditory memory storage and contains auditory memory cells [5].

The DLPFC is involved in the tinnitus distress network [81] as well as in processing of aversive sounds [48].

A single session of transcranial direct current stimulation (tDCS) over the DLPFC can transiently improve tinnitus intensity and tinnitus distress [82], in those patients who have increased activity in the subgenual, parahippocampal and auditory cortex [79]. The tDCS of the DLPFC activates the pregenual anterior cingulate cortex and inhibits gamma band activity in the parahippocampal and auditory cortex [78]. Repeated sessions exert more suppression than single sessions [19].

Gamma band activity in the auditory cortex has been linked to the perceived tinnitus loudness [76], and the parahippocampal area is involved both in tinnitus characteristics [77,84,85] as well as distress [13,81]. Based on these preliminary results, repetitive tDCS can potentially be used as a treatment for tinnitus [19,20].

In view of the transient nature of the tinnitus improvement, even in repetitive tDCS (rtDCS), a first successful attempt has been performed to implant an electrode on the right DLPFC for permanent tinnitus suppression [14].

Targeting the same area with transcranial magnetic stimulation (TMS) has only been performed in the setting of combined DLPFC and auditory cortex repetitive TMS (rTMS) [32,37], demonstrating that adding DLPFC to the auditory cortex rTMS yields better outcomes after 3 months, in comparison to exclusive auditory cortex rTMS [32]. However it is unknown whether rTMS of the DLPFC in itself is capable of modulating tinnitus perception.

Thus, a study was initiated consisting of 2 trials, one single session TMS trial, evaluating the difference between 1 and 10 Hz stimulation, and an open-label trial of rTMS. Both trials target the right DLPFC.

Methods

Both studies 1 and 2 have been approved by the Antwerp University Hospital IRB ('Comité voor medische ethiek'). Patients gave an informed consent.

Study 1

Participants

Forty-four patients (28 males and 16 females) with a mean ages of 51.61 years (Sd = 12.47) and who visited the multi-disciplinary TRI (Tinnitus Research Initiative) tinnitus clinic of the University of Antwerp, Belgium for tinnitus were initially included. Patients with a known history of epilepsy, pacemakers, cochlear implants, neurostimulators, or intracerebral pathology were excluded from the study. Fourteen patients had pure tone tinnitus, while 30 patients had narrow band noise. Twenty-three patients had bilateral tinnitus, while twenty-one patients had unilateral tinnitus. The mean tinnitus duration was 4.02 years (Sd = 3.75).

All participants underwent a complete audiological, otological and neurological investigation to rule out possible treatable causes for their tinnitus. Tinnitus matching is performed by presenting sounds to the ear in which the tinnitus is not perceived. Technical investigations include MRI of the brain and posterior fossa, pure tone and speech audiometry, and tympanometry. No patient had hyperacusis. The mean tinnitus frequency was 5288.64 Hz and the hearing loss at the tinnitus frequency was 8.76 dB SL.

TMS

TMS is performed as a routine neuromodulation technique in the treatment for tinnitus in the multidisciplinary TRI tinnitus clinic of the University of Antwerp, Belgium.

Table 1
Tinnitus characteristics for the patients assigned to 1 or 10 Hz stimulation for study 1.

		TMS protocol	
		1 Hz	10 Hz
Tinnitus type	Narrow band noise	8	6
	Pure tone	16	14
Tinnitus side	Unilateral	9	12
	Bilateral	15	9
Tinnitus duration	Mean	4.13	4.29
Hearing loss	Hz	5404.19	5149.97
	dB SL	8.02	9.64

The motor threshold to TMS was first determined as the lowest intensity sufficient to produce left thenar muscle activation in at least 5 of 10 trials with a single pulse delivered by placing the coil over the motor cortex using electromyography. The coil was positioned tangentially to the scalp and oriented so that the induced electrical currents would flow approximately perpendicular to the central sulcus, at 45° angle from the mid-sagittal line. When applying sham TMS with electrical stimulation to have a similar sensory effect this thus induces a partially active, albeit indirect neuromodulation effect. TMS is performed using a super rapid stimulator (Magstim Inc, Wales, UK) with a figure eight coil placed over the right dorsolateral prefrontal cortex. The intensity of the stimulation set at 80% of the motor threshold (MT). This threshold is used because it has been shown that 80% MT already modulates the ipsilateral auditory cortex (AC), whereas 100% MT has contralateral AC activation and 120% bifrontal activation [57]. Thus the minimal intensity known to still modulate the auditory cortex is 80% MT.

Patients were assigned randomly to the 1 Hz or 10 Hz condition. Twenty–four patients received 1 Hz stimulation, while twenty patients received 10 Hz stimulation. Each stimulation session consisted of 200 pulses. The presence of a control procedure (i.e. placebo effect) is tested by placing the coil perpendicular to the frontal area at the similar frequency. This sham method was elected because it has recently been shown that the effect of TMS and tDCS is mediated via a direct effect on the brain and an indirect effect via the trigeminal or C2 nerve [80]. Real- and sham TMSs were delivered in a random order. All patients were wearing earplugs during the TMS session. Table 1 shows the tinnitus characteristics for the patients assigned to 1 or 10 Hz stimulation.

Evaluation

A visual analog scale (VAS) for tinnitus perception ('How loud do you perceive your tinnitus? 0 = no tinnitus and 10 = as loud as imaginable') was asked before (pre) and directly after both sham and real TMS stimulation.

Statistical analysis

Calculations were performed using SPSS 15 (SPSS Unc, Chicago, IL) software package. A Repeated measures analysis of variance (ANOVA) was conducted with tinnitus perception at baseline, after sham and real treatments as within variable for both 1- and 10 Hz groups and with stimulation frequencies (1 vs. 10 Hz) as between variable to compare between the 2 groups.

Study 2

Participants

Eleven of the patients (9 males and 3 females) with a mean ages of 52 years (Sd = 10.49), namely those who responded to a single session of DLPFC 1 Hz TMS, were selected for rTMS. Patients who responded to sham stimulation in study 1 were excluded from study 2. Three patients had pure tone tinnitus, while seven patients

had narrow band noise. Seven patients had bilateral tinnitus, while four patients had unilateral tinnitus. The mean tinnitus duration was 3.82 years (Sd = 1.64). The mean tinnitus frequency was 4820.64 Hz (Sd = 2412.24 Hz) and the hearing loss at the tinnitus frequency was 7.04 dB SL.

The protocol was applied in a similar way as in study 1. All patients received 10 sessions, each time consisting of 600 pulses. Patients received rTMS stimulation every day of the week, 10 days in a row (expect for the weekend). Again a visual analog scale (VAS) for tinnitus perception was asked before (pre) and directly after rTMS stimulation.

Statistical analysis

As only 11 patients were included in the second study we applied a Wilcoxon Singed Ranks test.

Electroencephalography (EEG) study

The twenty-four patients who received 1 Hz TMS in study 1 underwent an EEG recording before receiving TMS. We divided these patients into responders versus non-responders based on their score on the VAS perception. Responders are defined as patients who experience a >10% improvement on VAS on the 1 Hz TMS (Baseline − Post TMS > 10%) and had no improvement on placebo stimulation. Non-responders are patients with <10% improvement (<10% VAS change) on 1 Hz TMS. Those patients who had a placebo response on sham stimulation are also considered non-responders. To compare differences in brain activity between the 1 Hz TMS responder group and the non-responder group, we performed source localization and functional connectivity analyses, described in more detail later.

In addition, this was also applied on the 11 patients who received multiple sessions of 1 Hz TMS in study 2.

EEG data collection

EEG recordings (Mitsar-201, NovaTech http://www.novatecheeg.com/) were obtained in a quiet and dimly lighted room with each participant sitting upright on a small but comfortable chair. This EEG system is used by several research groups over the world [52,63,72]. The actual recording lasted approximately 5 min. The EEG was sampled with 19 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1 O2) in the standard 10-20 International placement referenced to linked ears and impedances were checked to remain below 5 kΩ. Data were collected eyes-closed (sampling rate = 500 Hz, band passed 0.15–200 Hz). Data were resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 2–44 Hz and subsequently transposed into Eureka! Software [9], plotted and carefully inspected for manual artifact-rejection. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movement, or electrocardiography (ECG) artifact were removed from the stream of the EEG. Average Fourier cross-spectral matrices were computed for bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–44 Hz).

Source localization

Standardized low-resolution brain electromagnetic tomography (sLORETA) was used to estimate the intracerebral electrical sources that generated the scalp-recorded activity in each of the eight frequency bands [62]. sLORETA computes electric neuronal activity as current density (A/m^2) without assuming a predefined number of active sources. The sLORETA solution space consists of 6239 voxels (voxel size: 5 × 5 × 5 mm) and is restricted to cortical gray matter and hippocampi, as defined by digitized MNI152 template [21]. Scalp electrode coordinates on the MNI brain are derived from the international 5% system [28].

The tomography sLORETA has received considerable validation from studies combining LORETA with other more established localization methods, such as functional Magnetic Resonance Imaging (fMRI) [56,87], structural MRI [93], Positron Emission Tomography (PET) [16,65,98] and was used in previous studies to detect for example activity in the auditory cortex [83,85,94]. Further sLORETA validation has been based on accepting as ground truth the localization findings obtained from invasive, implanted depth electrodes, in which case there are several studies in epilepsy [95,97] and cognitive ERPs [89]. It is worth emphasizing that deep structures such as the anterior cingulate cortex [64], and mesial temporal lobes [96] can be correctly localized with these methods. In the current implementation of sLORETA, computations were made in a realistic head model [21], using the MNI152 template [46], with the three-dimensional solution space restricted to cortical gray matter, as determined by the probabilistic Talairach atlas [38]. The standard electrode positions on the MNI152 scalp were taken from [28] and [59]. The intracerebral volume is partitioned in 6239 voxels at 5 mm spatial resolution. Thus, sLORETA images represent the standardized electric activity at each voxel in neuroanatomic Montreal Neurological Institute (MNI) space as the exact magnitude of the estimated current density. Anatomical labels as Brodmann areas are also reported using MNI space, with correction to Talairach space [6].

Functional connectivity

Brain connectivity can refer to a pattern of anatomical links ("structural connectivity"), of statistical dependencies ("functional connectivity") or of causal interactions ("effective connectivity") between distinct units within a nervous system. The present research focuses on functional connectivity which captures deviations from statistical independence between distributed and often spatially remote neuronal units. Statistical dependence may be estimated by measuring correlation or covariance, spectral coherence or phase-locking. Functional connectivity is often calculated between all elements of a system, regardless of whether these elements are connected by direct structural links. Unlike structural connectivity, functional connectivity is highly time-dependent. Statistical patterns between neuronal elements fluctuate on multiple time scales, some as short as tens or hundreds of milliseconds. It should be noted that functional connectivity does not make any explicit reference to specific directional effects or to an underlying structural model.

Coherence and phase synchronization between time series corresponding to different spatial locations are usually interpreted as indicators of the "connectivity". However, any measure of dependence is highly contaminated with an instantaneous, non-physiological contribution due to volume conduction [61]. Hence, Pascual-Marqui [60], introduced a new technique (i.e. Hermitian covariance matrices) that removes this confounding factor. As such, this measure of dependence can be applied to any number of brain areas jointly, i.e. distributed cortical networks, whose activity can be estimated with sLORETA. Measures of linear dependence (coherence) between the multivariate time series are defined. The measures are expressed as the sum of lagged dependence and instantaneous dependence. The measures are non-negative, and take the value zero only when there is independence and are defined in the frequency domain: delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–45 Hz). Based on this principle lagged linear connectivity was calculated. Regions of interest were defined based on previous brain research on tinnitus (see Table 2 for overview).

Table 2
Regions of interest and their references.

Regions of interest	References
Dorsal anterior cingulate cortex	[13]
	[70]
Subgenual anterior cingulate cortex	[81]
	[13]
Dorsolateral Prefrontal cortex	[47]
Orbitofrontal cortex	[13]
	[81]
Insula	[13]
	[75]
(Para)hippocampus	[40]
	[13]
	[81]
Auditory cortex	[74]
	[92]
	[54]

Statistical analyses

The methodology used is non-parametric. It is based on estimating, via randomization, the empirical probability distribution for the max-statistic, under the null hypothesis comparisons [58]. This methodology corrects for multiple testing (i.e., for the collection of tests performed for all voxels, and for all frequency bands). Due to the non-parametric nature of the method, its validity does not rely on any assumption of Gaussianity [58].

sLORETA statistical contrast maps were calculated through multiple voxel-by-voxel comparisons in a logarithm of F-ratio. The significance threshold was based on a permutation test with 5000 permutations. A comparison made between the responders and non-responders was applied.

Connectivity contrast maps were calculated through multiple voxel-by-voxel comparisons using t-statistics. The significance threshold was based on a permutation test with 5000 permutations. Again a comparison was made between the responders versus non-responders.

Results

Study 1

A repeated measures ANOVA revealed a significant main effect for the within variable condition ($F = 6.06$, $P < .01$). A multiple comparison control revealed that real TMS ($M = 5.91$, Sd $= 1.97$) significantly differs from respectively baseline ($M = 6.42$, Sd $= 1.62$) and sham TMS ($M = 6.37$, Sd $= 1.66$). No significant differences were obtained between baseline and sham TMS. This main effect was however moderated by the TMS protocol applied. A significant interaction effect between condition and stimulation protocol was found ($F = 3.28$, $P < .01$; see Fig. 1). A simple contrast analysis for the 1 Hz stimulation protocol revealed a significant effect for the comparison baseline and real TMS ($F = 18.56$, $P < .001$) as well as sham TMS and real TMS ($F = 16.22$, $P < .001$). Our results demonstrated a significant decrease during real TMS ($M = 5.42$, Sd $= 2.08$) in comparison to baseline ($M = 6.33$, Sd $= 1.61$) and sham TMS ($M = 6.29$, Sd $= 1.65$). For the 10 Hz stimulation a simple contrast analysis yielded no significant difference between baseline, real and sham TMS. In addition, no main effect was found for the stimulation protocol applied.

Eleven patients responded to the 1 Hz TMS treatment, without a response to sham TMS, with a mean suppression (the percent reduction of VAS loudness relative to baseline) of 39.23%.

No significant adverse events were reported.

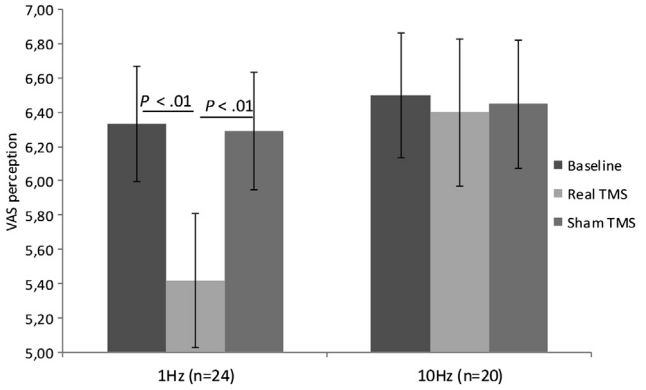

Figure 1. Mean scores on the VAS perception with error bars for baseline, real- and sham TMS after a single session. In the 1 Hz TMS group, VAS perception after real TMS was significantly decreased compared to those of baseline or sham TMS.

Study 2

A comparison between the baseline score and Post-rTMS revealed a significant effect ($Z = -2.03$, $P < .05$) indicting that after rTMS patients had an average decrease of 21.67% in VAS perception score (see Fig. 2). Seven of the eleven patients were considered responders (i.e. $>$ 10% tinnitus reduction) and had a mean suppression of 27.13%. The 4 patients who were considered as non-responders had no tinnitus suppression at all (0%).

No significant adverse events were reported.

EEG study

Brain activity using source localization analysis

A comparison between responders ($n = 11$) and non-responders ($n = 13$) for brain activity in the different frequency bands (i.e. delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–44 Hz)) yielded no significant effect, indicating that there are no differences in brain activity between the two groups.

In addition, a similar analysis was applied for the patients who underwent multiple sessions of DLFPC cortex (responders = 7 vs. non-responders = 4). Again no significant differences could be found.

Functional brain connectivity

A comparison in functional brain connectivity (= lagged phase synchronization) between responders ($n = 11$) and non-responders ($n = 13$) for the different frequency bands (i.e. delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma

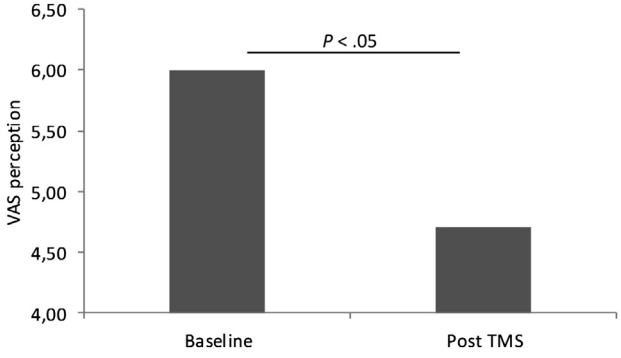

Figure 2. Scores on the mean VAS perception for baseline and post- TMS in 11 single TMS responders after multiple sessions.

(30.5–44 Hz)) demonstrated a significant effect. Our analysis revealed that responders had significantly more theta functional connectivity in comparison to non-responders between the right DLPFC, the left parahippocampus and the left primary and secondary auditory cortex. In addition increased functional connectivity was found between the left primary auditory and respectively the left and right anterior cingulate cortex, the left and right parahippocampus and right primary auditory cortex. The left and right anterior cingulate cortex also has more functional connectivity to the right parahippocampus and the primary and secondary auditory cortex (Fig. 3).

A similar analysis was applied for the patients that underwent multiple sessions of DLFPC cortex (responders = 7 vs. non-responders = 4). No significant differences could be found. However, it should be considered that this might be due to a lack of power, related to the relatively small sample size.

Discussion

The first trial demonstrates that TMS of the right dorsolateral prefrontal cortex is capable of suppressing tinnitus, but only for low frequency (1 Hz) stimulation, and the second trial shows that this benefit persists in multiple sessions. Thus it seems that the DLPFC can be used as a target for tinnitus modulation, both with electrical [19,20,78,82] and magnetic stimuli.

This opens the door for performing rTMS studies for tinnitus targeting the same areas as those involved in rTMS treatments for depression [73]. It is of interest that only 1 Hz rTMS of the right DLPFC benefits tinnitus perception. This is analogous to the modulatory effect of rTMS for depression. Whereas high frequency rTMS seems to be beneficial for depression when stimulating the left DLPFC [71], low frequency rTMS at 1 Hz seems to be better when targeting the right DLPFC [26]. It has been proposed that tinnitus and depression share a common pathophysiology [42]: neuroimaging and neuroendocrinological studies confirm the existence of neural circuits and neuroendocrinological changes that are activated both in depression and tinnitus. Impaired hippocampal neurogenesis has been documented in animals with tinnitus after noise trauma [36], as in animal models of depression. Finally, from investigations of human candidate genes, there is some evidence to suggest that variant BDNF may act as a common susceptibility factor in both disorders [42]. One possible confounder

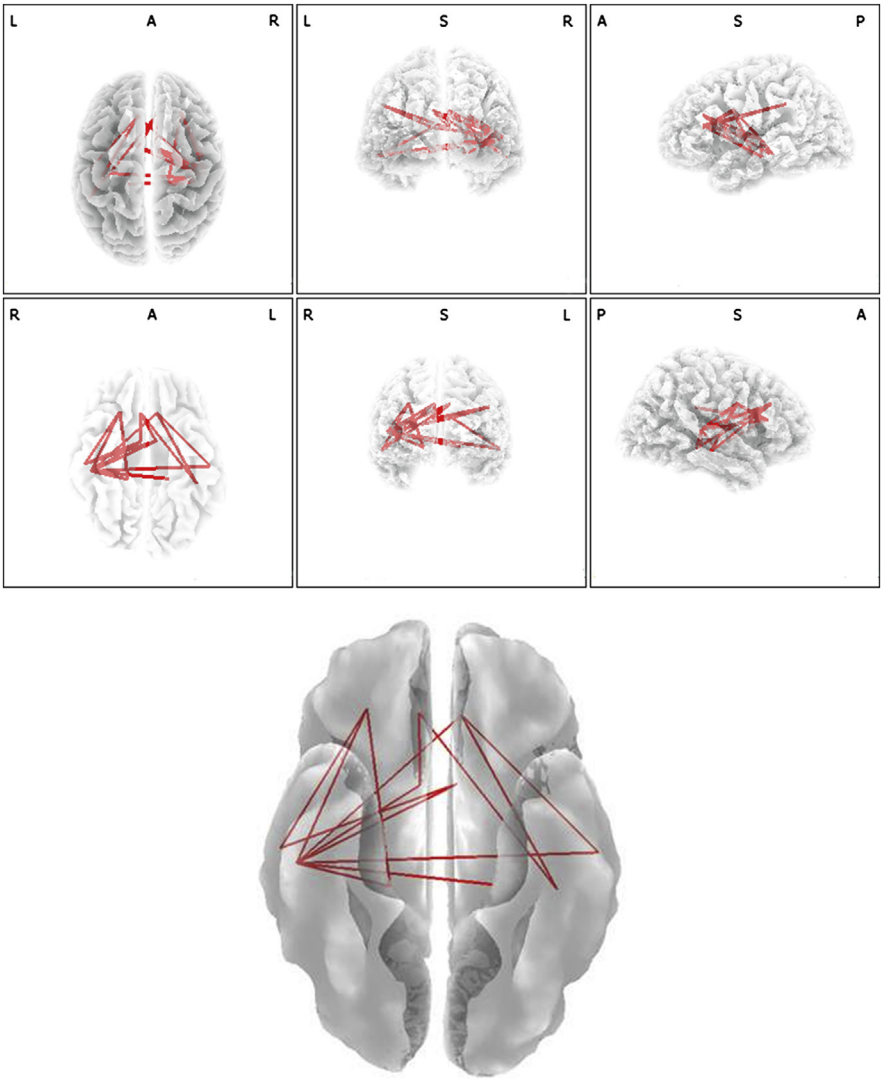

Figure 3. Pre-TMS functional connectivity (=lagged phase synchronization) of responders (n = 11) in comparison to non-responders (n = 13). Red lines represent functional connectivity that is significantly more present in responders than in non-responders to 1 Hz right DLPFC TMS for a single session (L: left side; R: right side; A: anterior side; P: posterior side). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

for this result might be related to the inherent differences in session duration between 1 Hz (more than 3 min for a session) and 10 Hz (20 s for a session). However, when one wants to control for that, the total amount of pulses for the 10 Hz becomes larger, resulting in another confounding factor. However, it should be considered that only 11 of 24 patients who underwent TMS responded in a sham controlled manner, and of those only 7 could be considered responders to multiple TMS sessions. The 11/24 response rate is similar to what is found in single session TMS studies performed for tinnitus targeting the auditory cortex [12,15,66,67]. By only selecting the placebo negative responders for the second study it is possible we introduced a negative bias. It cannot be excluded that when performing a study with multiple sessions of TMS comparing a sham group to a real stimulation group, that the results would not be better, also approaching the 40–50% response rate seen in rTMS studies [33,34,41,44].

The results for single session TMS are better than for multiple session TMS. This is related to the fact that of the 11 patients who responded to single session TMS, 4 did not respond to multiple session TMS. An explanation for this curious finding cannot yet be provided. No resting state brain activity or functional connectivity differences nor clinical differences could be discerned between the 7 responders to multiple TMS sessions versus the 4 patients who did not respond. A larger study should be performed to be able to do this. But it does signify that using a single session TMS as a prognosticator for therapeutic response of multiple sessions is not guaranteed at a single subject level, an issue which might have clinical importance.

The antidepressant effects of low frequency TMS in treatment-resistant depression may be associated with decreases in regional cerebral blood flow (rCBF) in the OFC and the subgenual cingulate cortex via the right prefrontal cortex [31]. This is similar to the effect exerted by bifrontal tDCS [78], which exerts its effect via functional connections with the parahippocampus and auditory cortex. The functional connectivity, as measured by lagged phase synchronization, differs between those patients who respond to DLPFC TMS and those who do not. This intuitively makes sense. The clinical effect of 1 Hz TMS of the right DLPFC seems to be mediated via functional connections between the DLPFC and a network consisting of the anterior cingulate, parahippocampus and auditory cortex. These areas have all been implicated in tinnitus and have been demonstrated in EEG studies in tinnitus [13,50,77–79,81,84–86].

It might not be incidental that especially theta lagged phase synchronization is critically involved in transmitting the stimuli to this auditory cortex-parahippocampal-anterior cingulate network. It has been proposed that low frequencies, such as theta are especially involved in long range connections [91], and auditory attention is mediated via theta synchronization of gamma frequencies present in spatially segregated areas involved in attentional control [17]. This fits with a general scheme in which theta is considered a carrier wave on which focal gamma band activity is nested to integrate and bind activity in spatially separated areas [8].

One Hz rTMS of the right DLPFC also modulates hypothalamic-pituitary-adrenal (HPA) axis functioning in depression [30], and in view of the HPA axis involvement in tinnitus [24,42] it should be investigated whether that also holds for tinnitus related distress.

In summary, 1 Hz rTMS of the right DLPFC transiently reduces the perceived tinnitus loudness, mediated via functional connections between the DLPFC and a network consisting of the anterior cingulate, parahippocampus and auditory cortex. Similar investigations should also look at how long the improvement lasts, whether there are any further differences between TMS responders and non-responders after TMS with regard to brain activity, and whether the tinnitus associated distress and depression can also be improved, as tDCS of the same area also changes the affective component of the tinnitus.

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